REMARKS/ARGUMENTS

Claims 1-3, 9-12, 17-19, 38-46, 48-52 and 54-64 are pending in the application. Claims 42, 48, and 54 have been amended. Support for the amendments can be found in the specification, particularly on page 32 at line 4 and lines 6-28. No new matter has been added by way of amendment. Reexamination and reconsideration of the claims are respectfully requested.

The Rejection of Claims Under 35 U.S.C.§112, First Paragraph, Should Be Withdrawn

The Office Action (12/03/03, page 2, #3) has maintained the rejection of claims 1-3, 9-12, 17-19, 38, 42-43, 46, 48-49, 52, and 54 and has rejected claims 55-64 under 35 U.S.C. §112, first paragraph, because:

> the specification, while being enabling for nucleic acids encoding SEQ ID NO:2 and 10, expression cassettes comprising the nucleic acid, plants and seeds comprising a construct comprising the nucleic acid and a method of using it to impact a plant pest, does not reasonably provide enablement for any nucleic acid that has 90% identity to SEQ ID NO:1, that hybridizes to SEQ ID NO:1 or that is antisense to a nucleic acid with 90% identity to SEQ ID NO:1....

As an initial matter, Applicants note that the rejections in the Office Action only refer to the claim limitation that requires nucleotide sequences to have at least 90% identity to SEQ ID NO:1. However, claims 38, 43, and 49, which are also encompassed by the rejection, contain limitations requiring the nucleotide sequence to have at least 95% identity to SEQ ID NO:1, while claims 55, 58, and 63 contain limitations requiring the nucleotide sequence to have at least 93% identity to SEQ ID NO:1 and claims 56, 59, and 64 contain limitations requiring the nucleotide sequence to have at least 94% identity to SEQ ID NO:1. The Office Action does not indicate that the differing scope of these dependent claims, i.e., these different levels of identity to the exemplary sequence of SEQ ID NO:1, were considered. Clarification is respectfully requested.

The Office Action (page 2) asserts that "Applicant's arguments...have been fully considered but they are not persuasive" and reiterates the grounds for rejection as in the previous

Office Action. In maintaining these grounds for rejection, the Office Action is disregarding not only Applicant's arguments but also the case law and guidelines cited in those arguments. Applicants respectfully traverse this rejection and submit that the Office Action is applying an extraordinarily high standard of enablement to the present claims, a standard that is not properly based on case law or on the statute.

In the previous Response, Applicants discussed that the claims are enabled by the disclosure. Applicants discussed (Response of May 29, 2003, particularly pages 14-16) that those of skill in the art, provided the guidance in the present specification, could readily make and use the invention. Applicants noted (Response of May 29, 2003, particularly pages 14-16) that those of skill in the art can readily determine the nucleic acid sequence of a nucleic acid molecule as well as the percent identity between sequences. In the instant specification, Applicants have provided assays and procedures by which those of skill in the art may readily determine whether a sequence meets the functional requirement of the claims. See particularly the specification at page 18, providing guidance regarding conservative substitutions of amino acids; pages 19-20 discussing the activity of variants; and pages 8, 29, 65-67, and 69, teaching methods for assaying pesticidal activity of proteins and providing working examples using these assays. Such assays are also known in the art. See, for example, Marrone *et al.* (1985) *J. Econ. Entomol.* 78:290-293 and Czapla and Lang (1990) *J. Econ. Entomol.* 83:2480-2485, which are incorporated by reference in the specification (p. 28). Thus, one of skill in the art would readily be able to make and use the claimed invention.

The enablement of the claimed invention is demonstrated by several working examples in which sequences sharing a relatively low percent identity to the exemplary of SEQ ID NO:1 are demonstrated to have pesticidal activity. In Example 4 (specification pp. 65-66), both the full-length endotoxin encoded by SEQ ID NO:1 and a truncated protein encoded by SEQ ID NO:15 were assayed for pesticidal activity against southern corn rootworm. The nucleotide sequence of SEQ ID NO:15 is a truncation of SEQ ID NO:1 which shares about 55% sequence identity with SEQ ID NO:1. In Example 6 (specification pp. 67-69), several truncated proteins were assayed and shown to have pesticidal activity against Colorado potato beetle (see Table 1, p. 68). These truncated proteins included those encoded by SEQ ID NO:15 and SEQ ID NO:19, which share

about 55% and 51% identity, respectively, to the exemplary nucleic acid sequence set forth in SEQ ID NO:1 (alignments performed using BLAST with default parameters). Another mutant assayed for pesticidal activity in Example 6 was NGSR1218-1 (encoded by SEQ ID NO:11). The NGSR1218-1 mutant includes the amino acid sequence "NGSR" inserted between amino acids 164 and 165 of the truncated endotoxin of SEQ ID NO:16. The nucleotide sequence encoding this mutant (SEQ ID NO:11) shares about 56% sequence identity with the exemplary nucleotide sequence of SEQ ID NO:1, yet both proteins have pesticidal activity. The specification also teaches an exemplary maize-optimized sequence (SEQ ID NO:9), which encodes the same pesticidal polypeptide as SEQ ID NO:15 but shares less than 69% sequence identity with it.

Thus, the specification is replete with working examples of sequences that share a low percentage of identity with SEQ ID NO:1 and which encode polypeptides having pesticidal activity. Applicants respectfully submit that the working examples provided in the specification show that the claimed invention could be readily made and used by those of skill in the art. The specification teaches how to make sequences sharing a relatively low percentage of sequence identity and how to assay those sequences for pesticidal activity. This presentation of multiple working examples illustrates that a number of sequences meet the functional requirement of the claims and also bolsters Applicants' arguments that such experiments are routine in the art.

In the previous Response (of May 29, 2003), Applicants discussed the appropriate standard for determining whether undue experimentation would be required to make and use an invention, including *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and *In re Jackson*, 217 USPQ 804, 807 (Bd. Pat. App. & Int. 1982). In *In re Jackson*, the Board held that a considerable amount of experimentation is permitted to practice the invention and is not undue if it is merely routine in the art or if the specification provides a reasonable amount of guidance and direction to perform such experimentation. Applicants again stress that when evaluating the quantity of experimentation required, the Federal Circuit looks to the amount of experimentation required to practice a single embodiment of the invention rather than the amount that would be required to practice ***every*** embodiment of the invention, as is assumed in the Office Action (see *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988); *Johns Hopkins University v. Cellpro*, 931 F. Supp. 303, 324

(D. Del. 1996), *aff'd in part, vacated in part, and remanded*, 47 USPQ2d 1705 (Fed. Cir. 1998) (stating that "[t]he specification need only enable one mode of making the claimed invention."))

Further, it is now customary in the art to make and assay a number of sequences for a desired function in order to achieve the best results. For example, such techniques can involve what is commonly referred to as "shuffling," as described for example in U.S. Patent No. 5,837,458, issued November 17, 1998 with inventors Minshull and Stemmer and entitled, "Methods and Compositions for Metabolic and Cellular Engineering." In such techniques, it is common to mutagenize individual sequences or a set of sequences which are then assayed for a desired activity. In fact, such techniques may even make use of a library of sequences which is recursively mutagenized, screened for function using a functional assay, and re-mutagenized in order to find a sequence exhibiting optimal function. Examples of the use of such techniques include: Minshull and Stemmer (1999) *Current Opinion in Chemical Biology* 3:284-290, entitled "Protein Evolution by Molecular Breeding"; and Christians *et al.* (1999) *Nature Biotechnology* 17: 259-264, entitled "Directed evolution of thymidine kinase for AZT phosphorylation using DNA family shuffling." Such experiments are designed and are intended to encompass the generation and testing of a very large number of variant sequences for a desired function. As indicated by these and other publications, this experimentation is now considered routine in the art and thus would not be considered "undue experimentation" under *In re Wands* and *In re Jackson*.

In light of the discussion above, it is apparent that those of skill in the art would be able to make and use a nucleic acid meeting both the sequence identity limitation of the claims and the functional requirement for pesticidal activity. As illustrated by the several working examples in the specification and by the state of the art, one of skill in the art would not consider the amount of experimentation required to be undue. Accordingly, this rejection of the claims for lack of enablement should be withdrawn.

The Office Action (12/03/03, page 4, point #4) has maintained the rejection of claims 1-3, 9-12, 17-19, 38, 42-43, 46, 48-49, 52, and 54 and rejected claims 55-64 under 35 U.S.C. §112, first paragraph:

> [A]s containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is repeated for the reasons of record.... Applicant's arguments...have been fully considered but they are not persuasive."

In maintaining these grounds for rejection, the Examiner disregards not only Applicants' arguments but also the case law cited in those arguments. Applicants respectfully submit that the Examiner is applying an extraordinarily high standard of written description to the present claims, a standard that is not properly based on case law or on the statute.

The Office Action states (12/03/03, page 4) that "Applicant has not described nucleic acids that hybridize to SEQ ID NO:1 AND that encode pesticidal proteins." (emphasis in original) The Office Action continues, "Applicant has not described even one nucleic acid that hybridizes to SEQ ID NO:1 AND that encodes a pesticidal protein or that has 90% identity to SEQ ID NO:1 AND that encodes a pesticidal protein." Applicants respectfully disagree with this conclusion. In contrast to this conclusion, the specification teaches a number of nucleic acids that share even lower percent identity with SEQ ID NO:1 and encode pesticidal proteins, as demonstrated with working examples.

The specification provides working examples in which sequences sharing a relatively low percent identity to the exemplary sequence of SEQ ID NO:1 are demonstrated to have pesticidal activity. In Example 4 (specification pp. 65-66), both the full-length endotoxin encoded by SEQ ID NO:1 and a truncated protein encoded by SEQ ID NO:15 were assayed for pesticidal activity against southern corn rootworm. The nucleotide sequence of SEQ ID NO:15 is a truncation of SEQ ID NO:1 which shares about 55% sequence identity with SEQ ID NO:1. In Example 6 (specification pp. 67-69), several truncated proteins were assayed and shown to have pesticidal activity against Colorado potato beetle (see Table 1, p. 68). These truncated proteins included those encoded by SEQ ID NO:15 and SEQ ID NO:19, which share about 55% and 51% identity, respectively, to the exemplary nucleic acid sequence set forth in SEQ ID NO:1 (alignments performed using BLAST with default parameters). Another mutant assayed for pesticidal activity in Example 6 was NGSR1218-1 (encoded by SEQ ID NO:11). The NGSR1218-1 mutant includes the amino acid sequence "NGSR" inserted between amino acids 164 and 165 of

the truncated endotoxin of SEQ ID NO:16. The nucleotide sequence encoding this mutant (SEQ ID NO:11) shares about 56% sequence identity with the exemplary nucleotide sequence of SEQ ID NO:1, yet both encoded proteins have pesticidal activity. The specification also teaches an exemplary maize-optimized sequence (SEQ ID NO:9), which encodes the same pesticidal polypeptide as SEQ ID NO:15 but shares less than 69% sequence identity with it. Thus, the present specification provides multiple working examples illustrating the production of sequences that encode pesticidal proteins and share a relatively low percentage of sequence identity with SEQ ID NO:1. Multiple working examples are presented, illustrating that Applicants were in possession of the invention at the time of filing.

Applicants respectfully submit that the present claims and specification meet the 35 U.S.C. §112 written description requirement as clarified by *Eli Lilly* and *Amgen*. See, *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997) and *Amgen Inc. v. Chugai Pharmaceutical Co.*, 18 USPQ2d 1016. As discussed in the previous Response (dated May 29, 2003, particularly pages 17-20), Applicants have provided exemplary sequences of the invention as set forth in SEQ ID NO:1. The claimed nucleic acids are defined in reference to the nucleotide sequence of SEQ ID NO:1, either by sequence identity or by hybridization. Applicants have thus provided a structural definition of the sequences of the invention. Applicants have also provided assays by which those of skill in the art can readily assess whether a nucleic acid molecule meeting the nucleotide sequence element of the claims also meets the functional limitation element of the claims. This is what *Eli Lilly* requires. Thus, Applicants have also conceived the sequences of the invention as articulated in *Amgen*; that is, Applicants are able "to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it." *Amgen*, 18 USPQ2d at 1021.

Applicants further note that the Federal Circuit has explicitly stated that:

> *Eli Lilly* did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure.

Amgen, Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1332, 65 USPQ2d 1385, 1398 (Fed. Cir. 2003). *See also, Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1320, 66 USPQ2d 1429, 1438 (noting that "[i]n more recent cases, however, this court has distinguished *Lilly"* and further noting that in *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 323 F.3d 956 (Fed. Cir. 2002), "neither the specification nor the deposited biological material recited the precise 'structure, formula, chemical name, or physical properties' required by *Lilly*.")

In light of the above statements, Applicants respectfully assert that the present specification does meet the statutory enablement and written description requirements. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection of the claims under 35 U.S.C. §112.

With regard to claims 42, 48, and 54, which are specifically discussed on page 4 of the Office Action, Applicants note that these claims have been amended to specify a time of hybridization and a wash temperature. Support for these amendments is found in the specification on page 32, lines 1-4 and lines 6-28.

Hybridization techniques are very well established in the art. As indicated on page 32, specificity is typically the function of post-hybridization washes, the critical factors being the ionic strength and temperature of the final wash solution. Thus, if one of skill desired the stringency of the wash conditions to be varied, the temperature or salt concentration would be altered. As evidence of this common understanding in the art, Applicants provide an excerpt from Moore and Dowhan, "Preparation and Analysis of DNA: Hybridization Analysis of DNA Blots," *Current Protocols in Molecular Biology*, 2002, Chapter 2.10.11, Supplement 26, John Wiley and Sons, New York. The excerpt concludes that the stringency of wash conditions are manipulated based on the T_m calculation and that the manipulation of stringency occurs via a change in temperature or salt concentration. This approach allows for the high level of reproducibility seen in the art as it relates to hybridization assays.

> *Designing washes for heterologous hybridization.* Calculations of T_m become more critical if heterologous probing is being attempted. If the aim is to identify sequences that are merely related, not identical, to the

> probe (*e.g.*, members of a multigene family, or a similar gene in a second organism), then it is useful to have an idea of the degree of mismatching that will be tolerated by a "moderate-" or "low-" stringency wash. The best way to approach this is to first establish the lowest temperature at which only homologous hybridization occurs with a particular SSC concentration. Then assume that 1% mismatching results in a 1°C decrease in the T_m (Bonner *et al.*, 1973) and reduce the temperature of the final wash accordingly (for example, if sequences with ≥90% similarity with the probe are being sought, decrease the final wash temperature by 10°C). If the desired degree of mismatching results in a wash temperature of <45°C, then it is best to increase the SSC concentration so that a higher temperature can be used. Doubling the SSC concentration results in a ~17°C increase in T_m, so washes at 45°C in 0.1xSSC and 62°C in 0.2xSSC are roughly equivalent. Note that in these extreme cases it may also be necessary to reduce the hybridization temperature to as low as 45°C (aqueous solution) or 32°C (formamide solution).

In view of the knowledge of the art, one of skill would recognize that a wash would be maintained until equilibrium was reached. One of skill would recognize that the length of the wash recited in claims 42, 48, and 54 is carried out for at least the length of time it is required to establish equilibrium. Wash time extending beyond equilibrium will not influence the outcome. Thus, the recitation of a specific temperature and salt concentration clearly define the stringency of the wash conditions.

Claims 42, 48, and 54 also contain limitations requiring that the nucleic acids have pesticidal activity. Because, as discussed above, assays for pesticidal activity are taught in the specification and are also known in the art, Applicants respectfully submit that these claims meet the written description requirement of 35 U.S.C. §112 and are in condition for allowance.

In view of the above comments and amendments, Applicants respectfully submit that all of the claims meet the written description of 35 U.S.C. §112 and are in condition for allowance.

The Rejection of Claims Under 35 U.S.C.§112, Second Paragraph, Should Be Withdrawn

The Office Action (12/03/03, page 6, #5) has rejected claims 42, 48, and 54 as being indefinite for reasons of record. These claims have been further amended to specify a time of

hybridization and a wash temperature. Support for these amendments can be found in the specification, for example, on page 32. Accordingly, this rejection should be withdrawn.

The Rejection of Claims Under 35 U.S.C. §102(b) Should Be Withdrawn

The Office Action (12/03/03, page 7, #6) has rejected claims 42, 48, and 54 under 35 U.S.C. §102(b) as anticipated by Michaels *et al.* (1996, U.S. Pat. No. 5,554,534). This rejection is respectfully traversed. Claims 42, 48, and 54 have been amended to recite additional high-stringency hybridization and wash conditions, as supported in the specification particularly on page 32. Applicants note that the sequence search results cited by the Examiner indicate a "query match" between SEQ ID NO:1 and the Michaels sequence of only 70.8%, and sequences sharing only 70.8% sequence identity would not be expected to hybridize to each other under high stringency conditions. Accordingly, the rejection of the claims under 35 U.S.C. §102 should be withdrawn.

Consideration Of Previously Submitted Information Disclosure Statement

It is noted that an initialed copy of the PTO Form 1449 that was submitted with Applicants' Information Disclosure Statement filed December 17, 2002 has not been returned to Applicants' representative with the Office Action. Accordingly, it is requested that an initialed copy of the Form 1449 be forwarded to the undersigned with the next communication from the PTO. In order to facilitate review of the references by the Examiner, a copy of the Information Disclosure Statement and the Form 1449 are attached hereto. Copies of the cited references were provided at the time of filling the original Information Disclosure Statement, and, therefore, no additional copies of the references are submitted herewith. Applicants will be pleased to provide additional copies of the references upon the Examiner's request if it proves difficult to locate the original references.

CONCLUSION

In view of the above amendments and remarks, Applicants submit that the rejections of the claims under 35 U.S.C. §§112, first and second paragraphs, and 102(b) are overcome.

Applicants respectfully submit that this application is now in condition for allowance. Early notice to this effect is solicited.

If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject Application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those, which may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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